UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/530,483 | 09/28/2005 | Joerg Rosenberg | 268305US0PCT | 5340 |

26474 7590 07/09/2008

NOVAK DRUCE DELUCA + QUIGG LLP
1300 EYE STREET NW
SUITE 1000 WEST TOWER
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| SASAN, ARADHANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 07/09/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

vincent.deluca@novakdruce.com
james.remenick@novakdruce.com
barbara.schwalge@novakdruce.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/530,483 | ROSENBERG ET AL. | |
| | Examiner | Art Unit | |
| | ARADHANA SASAN | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. The remarks and amendments filed on 3/19/08 are acknowledged.

2. Claim 1 was amended.

3. Claims 1-9 and new claims 10-20 are included in the prosecution.

### *Response to Arguments*

**Rejection of claims 1-9 under 35 USC § 103(a)**

4. Applicant's arguments with respect to the rejection of claims 1-9 under 35 USC § 103(a) as being unpatentable over Vladyka et al. (US 2002/0012706 A1) in view of Thacharodi et al. (EP 0 960 620 A1) have been fully considered and are found persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection, necessitated by Applicant's amendment of claim 1, is made in view of Klimesch et al. (US 5,073,379) in view of Carli (US 4,632,828), Endicott et al. (US 3,087,860) and Goertz et al. (US 4,801,460).

### *Claim Rejections - 35 USC § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 6-8 and 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klimesch et al. (US 5,073,379) in view of Carli (US 4,632,828).

The claimed invention is a process for producing solid dosage forms comprising forming a moldable cohesive composition which comprises:

a) 50 to 99.4% by weight of at least one crosslinked nonthermoplastic carrier,

b) 0.5 to 30% by weight of at least one adjuvant (selected from the group consisting of thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers) and

c) 0.1 to 49.5% by weight of at least one active ingredient.

The moldable cohesive composition is formed by heating at a temperature at or above the softening point of the adjuvant, but at least 70°C, in a multi-screw extruder and subsequently cooled.

Klimesch teaches "a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts" (Col. 1, lines 5-9). Klimesch teaches that "it is as a rule substantially more advantageous if the extruder is in the form of a conventional single-screw or multi-screw mixing extruder, so that premixing is unnecessary" (Col. 1, lines 31-34). "Shaping takes place directly after the extrusion process. The still plastic extrudate is passed, if necessary with the aid of a suitable guide channel ... through the shaping apparatuses ..." (Col. 1, lines 48-51). Klimesch teaches that "extrudable pharmaceutical mixtures are mixtures of one or more pharmaceutical active compounds with one or more auxiliaries which are conventionally used in the preparation of pharmaceutical tablets and are pasty and therefore extrudable due to the melting or softening of one or more components" (Col. 3, lines 1-

6). Pharmacologically acceptable polymers such as polyvinylpyrrolidone (PVP) and copolymers of N-vinylpyrrolidone (NVP) and vinyl acetate are disclosed (Col. 3, lines 6-12). Example 3 discloses crosslinked PVP as a tablet disintegrant (Col. 6, lines 52-53). Pharmacologically acceptable plasticizers such as fatty acid esters are disclosed (Col. 3, lines 29-38). Conventional pharmaceutical auxiliaries such as silicates, stearic acid or its salts with magnesium, lactose, cereal starch, corn starch or potato starch are also disclosed (Col. 4, lines 30-36). Active compounds are disclosed as substances having a pharmaceutical action and a very low level of side effects, provided that they do not decompose under the processing conditions, and the concentration of the active compound may be from 0.1% to 95% (Col. 4, lines 57-68 and Col. 5, line 1 to Col. 6, line 3). Theophylline is the active compound used in examples 1-14 (Col. 6, line 23 to Col. 8, line 21). Example 3 discloses: "47.5 parts of a copolymer having a K value of 30 and consisting of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, 2.5 parts of crosslinked PVP as a tablet disintegrant and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the five shots were each 120°C, and the die was at 130°C. The still plastic extrudate was pressed to give oblong tablets as in Example 1 (temperature of the double link belt: +15 °C). The tablets were stable to mechanical effects" (Col. 6, lines 49-59).

Klimesch does not expressly teach a high level (50-99.4%) of crosslinked nonthermoplastic carrier.

Carli teaches three different preparation techniques in which MAP (6$\alpha$-methyl, 17$\alpha$-hydroxy-progesterone acetate) is loaded in and on any swellable, water-insoluble

polymer (or combination thereof), such as for instance, cross-linked polyvinylpyrrolidone (cross-linked PVP) and cross-linked sodium carboxymethylcellulose (Col. 2, lines 4-12). The second method is heating of a mixture of the drug and the polymer up to melting temperature of MAP (Col. 3, line 62 to Col. 4, line 11). The weight ratios of MAP and the polymer in the mixture to be heated can vary from 1:0.1 to 1:100 w/w MAP: polymer (Col. 4, lines 16-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by Klimesch, combine it with the high level of polymer to drug ratio, as suggested by Carli, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Carli teaches that advantages of systems which consist of drugs loaded on hydrophilic, swellable, water-insoluble polymers include:

"1. Greater increases of drug wettability because of the greater hydrophilicity and swelling capacity in water of the hydrophilic, swellable, water-insoluble polymers.

2. More rapid disintegration in water of the system and faster dispersion of the drug particles. Some of the hydrophilic, swellable, water-insoluble polymers which may be used in the present process are, in fact, already used and marketed as disintegrants for oral solid dosage forms.

3. Avoidance of the viscous layer around the drug which can be associated with the use of water-soluble polymers and can hinder the drug diffusion and slow down the dissolution process" (Col. 2, lines 28-44).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 1, the limitation of the process of heating the components in a multi-screw extruder would have been obvious over the process of extruding a polymer melt containing the active compound and the multi-screw mixing extruder, as taught by Klimesch (Col. 1, lines 5-9 and Col. 1, lines 31-34). The limitation of forming a moldable cohesive composition would have been obvious over the plastic extrudate that was pressed to give oblong tablets (Col. 6, Example 3, lines 49-59). The limitation of the crosslinked nonthermoplastic carrier would have been obvious over the crosslinked PVP taught by Klimesch (Col. 6, Example 3, lines 52-53) and the cross-linked PVP and cross-linked sodium carboxymethylcellulose taught by Carli (Col. 2, lines 4-12). The weight percentage of the crosslinked nonthermoplastic carrier would have been obvious over the weight ratios of MAP and the polymer (1:0.1 to 1:100 w/w MAP: polymer) as taught by Carli (Col. 4, lines 16-19). One with ordinary skill in the art would use a high percentage of the polymer which functions as a disintegrant in order to optimize the desired release rate of the chose active ingredient. The limitation of the

adjuvant would have been obvious over the copolymers of N-vinylpyrrolidone (NVP) and vinyl acetate, as taught by Klimesch (Col. 3, lines 6-12). One with ordinary skill in the art would modify the level of adjuvant during the process of routine experimentation and the recited weight percentage of the adjuvant would have been an obvious variant over the 47.5 parts of the copolymer of NVP and vinyl acetate (taught by Klimesch) unless there is evidence of criticality or unexpected results. The limitation of the active ingredient would have been obvious over the active compounds that may be from 0.1% to 95%, as taught by Klimesch (Col. 4, lines 57-68 and Col. 5, line 1 to Col. 6, line 3).

Regarding instant claim 2, the limitation of the weight percentage of the crosslinked nonthermoplastic carrier would have been obvious over the weight ratios of MAP and the polymer (1:0.1 to 1:100 w/w MAP: polymer) as taught by Carli (Col. 4, lines 16-19). One with ordinary skill in the art would modify the level of thermoplastic polymer during the process of routine experimentation and the recited weight percentage of the thermoplastic polymer would have been an obvious variant over the 47.5 parts of the copolymer of NVP and vinyl acetate (taught by Klimesch) unless there is evidence of criticality or unexpected results. The limitation of the weight percentage of the solubilizer would have been obvious over the plasticizers taught by Klimesch (Col. 3, lines 29-38). One with ordinary skill in the art would use the plasticizers in order to ensure that the polymer/active mixture is extrudable and to modify the glass transition temperature accordingly (Klimesch, Col. 3, lines 29-38). The level of the plasticizers or solubilizers is a manipulatable parameter and the recited weight percentage would have been obvious variants during the process of routine optimization unless there is

evidence of criticality or unexpected results. The limitation of the active ingredient would have been obvious over the active compounds that may be from 0.1% to 95%, as taught by Klimesch (Col. 4, lines 57-68 and Col. 5, line 1 to Col. 6, line 3).

Regarding instant claim 3, the crosslinked nonthermoplastic carrier would have been obvious over the crosslinked PVP taught by Klimesch (Col. 6, Example 3, lines 52-53) and the cross-linked PVP and cross-linked sodium carboxymethylcellulose taught by Carli (Col. 2, lines 4-12).

Regarding instant claim 4, the thermoplastic polymer would have been obvious over the copolymers of N-vinylpyrrolidone (NVP) and vinyl acetate, as taught by Klimesch (Col. 3, lines 6-12).

Regarding instant claim 6, the lipid would have been obvious over the fatty acid esters (Col. 3, lines 29-38) and stearic acid (Col. 4, lines 30-36) as taught by Klimesch.

Regarding instant claim 7, the solubilizer would have been obvious over the fatty acid esters taught by Klimesch (Col. 3, lines 29-38).

Regarding instant claim 8, the limitation of the solubility of the active ingredient would have been obvious over the active compounds taught by Klimesch which include poorly water-soluble drugs such as betamethasone and acetylsalicylic acid (Col. 4, lines 57-68 and Col. 5, line 1 to Col. 6, line 3).

Regarding instant claim 10, the limitation of the tableting aid would have been obvious over the conventional pharmaceutical auxiliaries such as silicates, stearic acid or its salts with magnesium, lactose, cereal starch, corn starch or potato starch disclosed by Klimesch (Col. 4, lines 30-36).

Regarding instant claims 11-13, the limitations of components a) – c) that are mixed before heating, during heating and after heating would have been obvious over the process of mixing and extruding the components of the composition taught by Klimesch (Col. 6, lines 49-59). One with ordinary skill in the art would do this because during the process of routine experimentation the order of mixing and heating can be manipulated in order to achieve the desired attributes of the finished dosage form.

Regarding instant claim 14, the limitation of the moldable cohesive composition that is homogenized to distribute the active ingredient would have been obvious over the process of mixing and extruding the components of the composition taught by Klimesch (Col. 6, lines 49-59). One with ordinary skill in the art would ensure that the active ingredient was uniformly distributed in the composition by the process of mixing and extruding.

Regarding instant claim 15, the limitation of melting the adjuvant with the nonthermoplastic carrier and admixing the active ingredient would have been obvious over the process of extruding taught by Klimesch (Col. 6, lines 49-59) because during the process of routine optimization one with ordinary skill in the art would modify the order to adding the active ingredient to the other components in order to ensure uniformity.

Regarding instant claims 16-17, the residence time would have been obvious over the extrusion process taught by Klimesch (Col. 6, lines 49-59) because the residence time is a manipulatable parameter and one with ordinary skill in the art would increase or decrease the residence time of the composition in the multi-screw extruder

during the process of routine experimentation. The recited residence time frames would have been obvious variants unless there is evidence of criticality or unexpected results.

Regarding instant claim 18, the limitations of shaping the molded cohesive composition between at least one belt and at least one roll would have been obvious over the extrusion of a polymer melt containing an active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by Klimesch (Col. 1, lines 5-9).

Regarding instant claim 19, the limitations of shaping the molded cohesive composition by calendaring would have been obvious over the calendaring taught by Klimesch (Col. 1, lines 10-12).

7. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klimesch et al. (US 5,073,379) in view of Carli (US 4,632,828) and Endicott et al. (US 3,087,860).

The teachings of Klimesch and Carli are stated above.

Klimesch and Carli do not expressly teach sugar alcohols as adjuvants.

Endicott teaches adjuvants such as sorbitol and mannitol (Col. 3, lines 67-70) and teaches that a drug-plastic combination can be mixed and extruded (Col. 4, lines 21-23).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by

Klimesch, combine it with the high level of polymer to drug ratio, as suggested by Carli, further combine it with the use of adjuvants such as sorbitol and mannitol in an extrudable drug/plastic composition, as taught by Endicott, and produce the instant invention.

One of ordinary skill in the art would have done this because sugar alcohols such as sorbitol and mannitol are known in the art to be used as excipients or adjuvants and can be included in extrudable compositions, as evidenced by the teaching of Endicott.

Regarding instant claim 5, the limitation of the sugar alcohol would have been obvious over the sorbitol and mannitol taught by Endicott (Col. 3, lines 67-70).

8. Claims 9 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klimesch et al. (US 5,073,379) in view of Carli (US 4,632,828) and Goertz et al. (US 4,801,460).

The teachings of Klimesch and Carli are stated above.

Klimesch and Carli do not expressly teach the cooled composition that is comminuted and compressed to the dosage form.

Goertz teaches a process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and subjecting the mixture to extrusion and shaping, wherein the fusible binder used is a solvent-free NVP polymer (Col. 1, line 64 to Col. 2, line 4). "Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hotface cutting to give granules or

molding to give tablets … cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets" (Col. 5, lines 11-20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by Klimesch, combine it with the high level of polymer to drug ratio, as suggested by Carli, further combine it with the cold-face cutting to give granules, as taught by Goertz, and produce the instant invention.

One of ordinary skill in the art would have done this because Goertz teaches the formation of tablets from the granules.

Regarding instant claim 9, the limitation of the cooled composition that is comminuted and compressed to the dosage form would have been obvious over the granules formed from the extruded composition, as taught by Goertz (Col. Col. 5, lines 11-20).

Regarding instant claim 20, the limitation of hot or cold cutting to form small-particle granules would have been obvious over the hot or cold cutting to form granules of the extruded composition, as taught by Goertz (Col. Col. 5, lines 11-20).

***Conclusion***

9. No claims are allowed.

10. Since this new rejection was necessitated by applicant's amendment, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615